REVIEW ARTICLE

Covid 19: A Review of Existing Literature

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BACKGROUND

On the doorstep of 2020, 44 cases of pneumonia of unknown etiology were reported within 4 days in Hubei province of Wuhan city of China. Chinese authorities identified a new type of Coronavirus first on 7 January 2020 and the outbreak was associated with exposures in one seafood market in Wuhan city. First laboratory confirmed case of SARS-Cov-2 (previously named 2019-n CoV) outside china was reported in Thailand with travel history to Wuhan, China on 13 January. Japan reported a case of SARS-CoV-2 on 15 January. South Korea reported similar case with history of travel from Wuhan on 20th Jan 2020[1].

In the span of 1 month, 20 countries were affected with having total 9826 confirmed cases worldwide including 9720 cases in China and 106 cases in other 19 countries. WHO declared the outbreak to be a public health emergency of international concern on 30 January and was declared as a Global Pandemic on 11 March 2020[2]. India reported first confirmed case on 30 January in Kerala with travel history from Wuhan[3].

As of Jan 10, 2021 data shows 8,83,87,352 cases globally with case fatality rate of 2.17% with a total of 19,19,204 deaths[4]. In Europe, the total numbers of cases were reported to be 28 797 583with case fatality rate of 2.1%. USA is worst hit country and with 3,88,61,668 cases. India has second highest number of cases (1,04,50,284) with case fatality rate of 1.44%[4]. In India, the worst hit state is Maharashtra.

VIRUS STRUCTURE, INFECTION AND PATHOPHYSIOLOGY

Coronaviridae are enveloped positive sense single stranded RNA viruses of 30kb. Among the 4 genera of alpha, beta, gamma, delta, alpha and beta coronaviruses infect mammals. SARS-CoV, Middle East Respiratory Syndrome virus and SARS-CoV2 belong to beta coronaviridae[5].

Surface projections- a structural protein called spike is composed of transmembrane trimetric glycoprotein protruding from viral surface, which determines the diversity of coronavirus and host tropism. Angiotensin converting enzyme (ACE-2) is a functional receptor for SARS-CoV; however, high ACE2 was highly expressed in lung, heart, ileum, kidney and bladder. Spike comprises of two functional subunits; S1 subunit binds to host cell receptor and S2 subunit is for fusion of viral and cellular membranes. The coronavirus spike is unusual among viruses because a range of protease can cleave and activate it. Unique to SARS-CoV-2 is the existence of "Furin" cleavage site (RPPA sequence) at S1/S2 site, which makes the virus extremely pathogenic. Immune mediated inflammation plays a pivotal role in secondary viremia. Severity is associated with progressive lymphopenia and neutrophilia. Reports are also suggestive of reduced lymphocyte count, elevatedferritin, IL-6 and D-Dimer were associated with increased mortality. Cytotoxic lymphocytes such as cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells are necessary for the control of viral infection; however, functional exhaustion of cytotoxic lymphocytes is correlated with disease progression[6].

Cytokine storm: Evidence suggests the role of multiple proinflammatory cytokines, including IL-6, IL-10, G-CSF, Monocyte chemotactic protein 1. Macrophage inflammatory protein 1(MIP1) alpha TNF and CRP[7].

Hypercoagulability and thrombus formation: SARS-CoV-2 causes endothelial injury to pulmonary

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vasculature[8] that plays a central role in pathogenesis of ARDS and multiorgan failure. Vascular changes include diffuse alveolar damage and formation of fibrin thrombi. The lungs from patients with covid-19 had significant new vessel growth through a mechanism of intussuseptive angiogenesis[9]. Evidence suggests increase in factor VIII, fibrinogen, circulating prothromboticmicroparticles, neutrophil extracellular traps (NETs) and hyperviscosity causes hypercoagulable state in turn leading to Diffuse Intravascular Coagulation(DIC) leading to ARDS and multiorgan failure[10].

CLINICAL CHARACTERISTICS

COVID-19 primarily spreads through the respiratory tract, by droplets, respiratory secretions, and direct contact. Respiratory illness can range from a mild respiratory infection to a life threatening pneumonia and ARDS. Majority of SARS-CoV-2 infected individuals (80%) are asymptomatic or present mild symptoms[11]. On the other end, symptomatic individuals may evolve to more severe symptoms and even death.1099 laboratory-confirmed cases, found that the common clinical manifestations included fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), and headache (13.6%)[12]. Among hospitalized patients with COVID-19 complications such as pneumonia, sepsis, respiratory failure, and acute respiratory distress syndrome (ARD) are frequently found[13]. Although observational studies reported older age and the presence of comorbidities as risk factors for increased disease severity in patients with COVID-19, it rapidly became clear that severe disease can also occur in younger patients with no pre-existing medical conditions[14].

DETECTION METHODS:

Nucleic acid detection

Nucleic acid detection technology has the characteristics of early diagnosis, high sensitivity and specificity. 'Diagnosis and Treatment Guideline of the Novel Coronavirus Pneumonia' of China proposed to use fluorescent-tagged probe based real-time RT-PCR to detect SARS-CoV-2 nucleic acid in respiratory specimens or blood specimens[15].

Antibody detection

Many serological tests for covid-19 have become available in a short period as they might be cheaper and easy to implement at point of care. A recent systematic review and meta-analysis assessed the diagnostic accuracy of serological tests for SARS-CoV-2 infection[16]. Sensitivity was higher at least three weeks after symptom onset (ranging from 69.9% to 98.9%) compared with within the first week (from 13.4% to 50.3%). This means of those tested for covid-19 within one week of symptom onset, on average 44% to 87% will be falsely identified as not having infection. Thus current serological tests for covid-19 have limited utility in the diagnosis of acute covid-19.

PREVENTION:

To date, no effective vaccination is available. The risk of acquiring secondary and atypical infections is more so in cases of immune compromised individuals. Therefore, the best way in order to protect oneself is to follow the conventional infection control protocols and avoid unnecessary travel, public transport, contact with sick people and so on.

Appropriate use of face mask

N95 is a good fit mask preventing the entry of droplets and thereby minimizing the chance of acquiring the infection.

Decontamination of N95 respirators

- Ultraviolet light
- Hydrogen peroxide vapor - The U.S FDA has granted an emergency use authorization for use of low temperature vaporous hydrogen peroxide sterilizers, used for medical instruments to decontaminate N95 respirators[17].
- Moist heat - Moist heat was applied by preparing a container with one liter tap water in bottom and dry horizontal rack above water, container was sealed and warmed in an oven to 65 degree Celsius for atleast 3 hours and then opened, the respirator placed on the rack, and the container resealed and placed back in oven for additional thirty minutes[18].

CURRENT THERAPEUTIC TREATMENT

DRUG EVOLUTION

Given the lack of effective antiviral therapy against SARS-Cov-2, current treatments are mainly focused on symptomatic relief and respiratory support. Finding drugs that can bind to the viral protein and stop them from working is a logical way forward. The laborious, decade

long, classic pathway for the discovery and approval of new drugs could be less suited to the present pandemic. Repurposing existing drugs offers a potentially rapid mechanism to finding cures for unforeseen diseases, since the pharmacokinetics and safety profiles are known.

ANTIVIRALS-

Hydroxychloroquine

- It has several antiviral properties including inhibition of inflammatory cytokines such as IL-1, IL-6 and TNF-alpha.
- It also inhibits SARS-CoV-2 entry by changing the glycosylation of ACE2 receptor and spike protein.
- HCQ can block the endosome maturation at intermediate stages of endocytosis, resulting in failure of virion transport to releasing site.

While initial evidence pointed towards efficacy of hydroxychloroquine in decreasing the clinical severity of disease and prophylaxis, later evidence has found limited role of HCQ does not result in reduction of mortality of hospitalized patients. A recent systematic review was conducted with the objectives of evaluation of safety and efficacy of HCQ. It included seven studies (n=1358) and no difference was observed in virological cure (OR, 2.37, 95% CI, 0.13-44.53), death or clinical worsening of disease (OR, 1.37, 95% CI, 1.37-21.97), and safety (OR, 2.19, 95% CI, 0.59-8.18), when compared with the control/conventional treatment[19].

Remdesivir

Remdesivir exhibits broad-spectrum antiviral activity against RNA viruses like Ebola virus (EBOV) and Middle East respiratory syndrome coronavirus (MERS-CoV). Remdesivir has been reported to inhibit viral RNA synthesis by a specific mechanism of delayed chain termination[20]. It has been used in the dose of 200 mg administered intravenously on day 1, ensued by 100 mg daily for the remaining days for a total of 5-10 days.

Contraindications:

- AST/ALT > 5 times Upper limit of normal (ULN)
- Severe renal impairment (i.e., eGFR< 30ml/min/m^2 or need for hemodialysis)
- Pregnancy or lactating females
- Children (< 12 years of age)

Lopinavir+Ritonavir

Lopinavir and ritonavir are protease inhibitors which disrupt the process of viral replication and release from host cells while ritonavir additionally inhibits enzyme cytochrome P450 3A and therefore increases the half-life of lopinavir.Based on currently available data, there is no clear benefit for the use of lopinavir-ritonavir compared to standard of care in severe COVID-19[21].

Favipiravir

Favipiravir acts by inhibition of RNA-dependent RNA polymerase enzyme which is used in transcription and replication of the viral genome.

In an open-label non-randomized control study conducted by Q Cai et al, favipiravir (FPV) 1600 mg twice daily as a loading dose and 600 mg twice daily plus interferon (IFN)-α 5 million U twice daily by aerosol inhalation were administered to 35 patients with a median age of 43 (35.5–59) years[22]. They observed a shorter viral clearance time and significant improvement in chest imaging in FPV group with few adverse reactions.Currently there are 32 clinical trials under various phases of development for the use of favipiravir for COVID-19[23].

IMMUNOMODULATORY AGENTS

Cytokine storm has been associated with severity of disease. Studies have also shown that expression of IL-2R and IL-6 in serum appears to predict the severity and prognosis. Hence, combined treatment of an immunomodulatory agent to reduce the cytokine storm along with an antiviral agent may show promising results. Elevated levels IL-6 is a predictor of worst outcome in patients with covid-19.

A. Tocilizumab

Monoclonal antibody against IL-6 blocks the signal transduction and has been considered in patients with elevated levels of IL-6.

Tocilizumab (Off Label) may be considered in patients with moderate disease with progressively increasing oxygen requirements and in mechanically ventilated patients not improving despite use of steroids. Long term safety data in COVID 19 remains largely unknown. It is administered in the dose of 8mg/kg (maximum 800 mg at one time) given slowly in 100 ml normal saline over 1 hour; dose can be repeated once after 12 to 24 hours if needed[24].

Special considerations before its use include:

- Presence of raised inflammatory markers (e.g., CRP, Ferritin, IL-6)

- Patients should be carefully monitored post Tocilizumab for secondary infections and neutropenia.
- Active infections and Tuberculosis should be ruled out before use.

B. Interferon-beta(IFN-beta)

Interferons modulate both T-and B-lymphocyte responses by promoting the proliferation of memory T-cells, stimulating the differentiation of Th1 cells, inducing IFN-γ secretion from T-cells, and promoting isotype switching in B cells and differentiation into plasma cells.

They have widespread potential as therapeutic agents for viral infections. IFNs inhibit viral infection by preventing viral entry into target cells and by blocking different stages of the viral replication cycle for different viruses.

A prospective non controlled trial done by Farzaneh Dastan[25] et al showed resolution of fever within first 7 days in all patients and significant decrease within 10 days and recovery in imaging study after 14 days in all patients.

An open label randomized phase 2 trial conducted by Ivan Fan-Ngai Hung et al concluded that early triple antiviral therapy was safe and superior to lopinavir–ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19[26]. Future clinical study of a double antiviral therapy with interferon beta-1b as a backbone is warranted.

C. Low dose steroids

Glucocorticoids may modulate inflammation-mediated lung injury in Covid-19 and thereby reduce progression to respiratory failure and death. The preliminary results of the controlled, open-label Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial[27] of dexamethasone in patients hospitalized with Covid-19 provide evidence that treatment with dexamethasone at a dose of 6mg daily for up to 10 days reduces 28-day mortality among those who are receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.

An interventional randomized clinical trial[28] comparing High Versus Low Dose Dexamethasone for the treatment of COVID-19 Related ARDS is currently under phase 3.

ANTITHROMBOTIC THERAPY

Low molecular weight heparin (LMWH)

As evident in a meta-analysis of four published studies, derangement of coagulation parametershas been found be common in patients with severe form of COVID-19 infection and associated with a poor prognosis[29]. In these patients, low molecular weight heparin (LMWH) or unfractionated heparin (UFH) at doses registered for prevention of venous thromboembolism (VTE) seemed to be associated with a lower risk of death[30] and is currently recommended by the World Health Organization[31].

CONVALASCENT PLASMA TRANSFUSION

Immune (i.e. "convalescent") plasma refers to plasma that is collected from individuals following resolution of infection and development of antibodies. Passive antibody administration through transfusion of convalescent plasma may confer immediate immunity to susceptible individuals. Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events[32].

OXYGEN THERAPY AND RESPIRATORY SUPPORT

Respiratory failure is the primary organ dysfunction, which worsens the prognosis of COVID-19 patients. Oxygen therapy and respiratory support are the key treatments for COVID-19-induced ARDS. Hypoxemia is the hallmark of the pulmonary derangement of the disease, in fact a case series of COVID-19 patients demonstrated the presence of significant hypoxemia with no signs of respiratory distress (*"silent hypoxemia"*)[33].

For spontaneously breathing patients with mild-to-moderate dyspnea and hypoxemia, non-responsive to regular low-flow nasal cannula, initial approach may involve the use of high flow nasal cannula (HFNC) and awake prone positioning based on limited clinical data. HFNC, although initially controversial due to its aerosolizing potential, it was found to be safe in further studies, with a bio-aerosol dispersion not significantly different from regular nasal prongs[34].

NIV support (continuous positive airway pressure [CPAP] or Bi-level positive airway pressure [BiPAP]) has been employed in COVID-19 patients as a last resource to circumvent endotracheal intubation after failing HFNC and awake prone positioning, although no formal recommendation regarding their use has been released.

For COVID-19, there is no sufficient evidence to prove that HFNC is superior to NIV.

It is paramount to closely monitor the respiratory efforts in COVID-19 patients spontaneously breathing (regardless of the use of HFNC or NIV support). Institution of endotracheal intubation and mechanical ventilation should be made as soon as possible regardless of the phenotype of the COVID-19 pneumonia, when signs of respiratory distress are associated to the severe hypoxemia[35].

Prone positioning has been advocated in intubated patients with Covid-19 associated ARDS (CARDS). Pan et al. demonstrated increased lung recruitability and PaO2/FiO2 improvement after prone positioning in patients with moderate CARDS[36]. Prone positioning leads to a relieve of severe hypoxemia due to reduction of overinflated lung areas, promoting of alveolar recruitment and decreasing ventilation/perfusion mismatch.

CONCLUSION

The current COVID-19 pandemic has become an international public health problem. There have been rapid advances in what we know about the virus, its transmission and how it causes illness and clinical characteristics and management of COVID-19. Currently, a vaccine is not available, neither is a specific antiviraltreatment. Early identification of suspect cases, isolation, infection control, and providing symptomatic care are vital for overcoming the pandemic.

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Clinical Guidance for Management of Covid-19 Suspect / Confirmed Cases

Covid -19 Suspect / Confirmed Case
Stratification on the basis of disease severity

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Mild	Moderate	Severe
(Fever / Upper Respiratory Tract Infection)	• Pneumonia with no signs of severe disease • RR ≥ 24 / min, SpO_2 < 94% on room air	Respiratory distress requiring mechanical ventilation (non-invasive & invasive) RR ≥ 30 / min, SpO_2 < 90% on room air
Admit to Covid Care Center (CCC) / Home Isolation	**Admit in Dedicated COVID Health Centre (DCHC)**	**Admit in Dedicated COVID Hospital (DCH)**
• Contact and droplet precautions • Strict hand hygiene • Symptomatic management • Tab HCQ (400 mg BD x 1 day f/b 400 mg OD x 4 days) may be considered in patients with high-risk features[1] – preferably after shifting to DCHC or at home under strict medical supervision • **For home isolation patients**, seek medical attention when following warning symptoms/signs occur: o Difficulty in breathing o Persistent pain/ pressure in the chest o Mental confusion or inability to arouse o Developing bluish discoloration of lips / face o Decreased urine output o As advised by treating medical officer	**Oxygen Support** • Target SpO_2: 92-96% (88-92% in patients with COPD) • Preferred device for oxygenation: Non-rebreathing face mask (if HFNC or simple nasal cannula is used, N95 mask should be applied over it) • Awake Proning may be used as a rescue therapy (NIH protocol) • All patients should have daily 12-lead ECG • Follow CRP, D-dimer & Ferritin every 48-72 hourly (if available); CBC with differential count, Absolute Lymphocyte count, KFT/LFT daily • Tab HCQ (400 mg BD x 1 day f/b 400 mg OD x 4 days) after ECG Assessment • Consider IV methylprednisolone 0.5 to 1 mg/kg for 3 days (preferably within 48 hours of admission or if oxygen requirement is increasing) **Anticoagulation** • Prophylactic dose of UFH[2] or LMWH[2] (e.g. enoxaparin 40 mg daily SC) **Monitor for & shift to DCH** if any of the following occurs: • Increased Work of breathing (use of accessary muscles) • Hemodynamic instability • Increase in oxygen requirement	• Cautious trial of CPAP with oro-nasal mask / NIV with helmet interface/HFNC, if work of breathing is low • Maintain euvolemia • Consider IV methylprednisolone 1 to 2 mg/kg per day for 5-7 days (in 2 divided doses), if not given already • High prophylactic dose of UFH or LMWH (e.g. enoxaparin 40 mg or 0.5 mg/kg BD SC) if not at high risk of bleeding[3] • Consider intubation if work of breathing is high / not tolerating NIV[4] **Ventilator management** • Use conventional ARDSnet protocol (LTV, proning, etc.) • If sepsis / septic shock: Manage as per existing protocol and local antibiogram • Use sedation and nutrition therapy as per existing guideline

Testing
While attending suspect case as per above protocol based on clinical assessment, testing shall be resorted to & if negative - manage in a non-Covid facility according to clinical diagnosis

Discharge
After clinical improvement, discharge as per discharge policy

Investigational Therapies[5]
Remdesivir (EUA), Tocilizumab (Off label) & Convalescent plasma (Off label)

1 **High-risk patients for severe disease** include:
- o Age: 60 years or more
- o Hypertension, DM (diabetes mellitus) & other immunocompromised states
- o Chronic lung / kidney / liver disease
- o Cerebrovascular disease
- o Obesity (BMI > 25 kg / m2)

2 **LMWH:** Low Molecular Weight Heparin: if no contraindication or high risk of bleeding; **UFH:** Unfractionated heparin
3 **Risk of bleeding:** use validated score for assessing bleeding risk (eg HAS-BLED score)

3 Use D-dimer and SIC score for **further risk stratification** (SIC score ≥4 portends high thrombotic risk)
3 Follow AHA/ESC and ISTH guidelines in case patient is **on antiplatelet agents**
4 **Higher chances of NIV failure**
5 Informed and shared decision making is essential before prescribing any of these therapies